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(71) Applicant *(for all designated States except US)*: CORNING INCORPORATED [US/US]; 1 Riverfront Plaza, Corning, NY 14831 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: DANNOUX, Thierry, L., A. [FR/FR]; 18, résidence du Bel-Ebat, F-77210 Avon (FR).

(74) Agent: HERZFELD, Alexander, R.; Corning Incorporated, Patent Dept., SP FR 02-12, Corning, NY 14831 (US).

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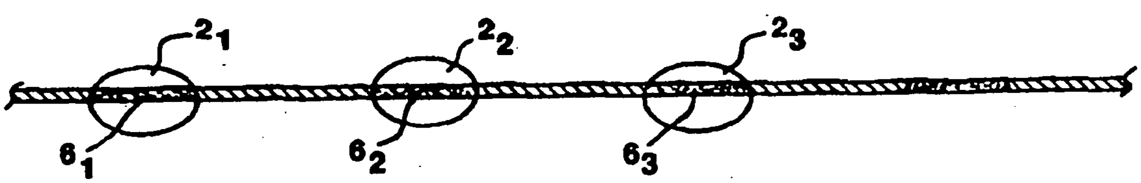

(57) Abstract

The tool (1, 3) is designed for the transport of drops (2_i) which are arranged according to a predetermined spatial distribution. It comprises at least one filiform support (1) mounted on a frame (3) clearing this support, said support presenting a plurality of the areas wettable by said liquid, distributed according to a predetermined distribution over its length, these wettable areas being separated from each other by nonwettable sections of said support (1). Application to cell cultures or tests on biological molecules.

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TOOL FOR THE TRANSPORT OF LIQUID DROPS AND METHOD FOR THE TRANSFER OF DROPS USING SUCH A TOOL

BACKGROUND OF INVENTION

The present invention relates to a tool for the transport of liquid drops and to a method for the transfer of such drops, from or into a network of miniature wells which can hold them.

To carry out tests or cultures on biological molecules or eukaryotic or prokaryotic cell cultures, plates molded of thermoplastic materials, such as a polycarbonate or polystyrene, are routinely used today, for example, cultivation cells and their nutrient medium. Typically, the rectangular plate has dimensions of approximately 80 x 125 mm, and the wells have a diameter of approximately 8 mm. These dimensions are standardized so as to allow the automatic manipulation of the plates in apparatuses such as a liquid manipulating robot, a reader for reading the plate by spectrophotometry, fluorimetry, or chemiluminescence determination, or an observation microscope. The wells are filled by means of a set of pipettes which are moved manually, a long and tedious procedure, or automatically. Samples of the products formed in the wells are collected, for example, using a

set of stainless steel needles or plastic tips which are immersed in the wells.

Today, the use of plates having an increasingly large number of wells per plate is being considered, for example, 384 or 1536 wells, and even plates comprising some ten thousand miniature wells, or microwells, per centimeter square of the plate surface area, as described in French Patent Application No. 95 13878 filed November 22, 1995 by the applicant. In the latter case, the wells, having a diameter on the order of 20-50 μm and a depth of 15-30 μm are distributed, with a separation on the order of

100 μm. It is conceivable that such dimensions make it practically impossible to load the wells with the sets of pipettes, or to collect samples from the wells with sets of metallic fingers, because of the extreme miniaturization, to a degree which is impossible to achieve, which would be required for these mechanical devices.

SUMMARY OF INVENTION

The present invention thus has the purpose of providing a tool for the transport of liquid drops into or from a network of microwells distributed with a very small separation making the use of the classic means of transport indicated above impossible.

Another purpose of the present invention is to provide such a tool which allows the simultaneous and automatic loading and unloading of at least a part of the wells of the network.

Yet another purpose of the present invention is to supply a method for the transfer of a plurality of liquid drops between microwells presenting a predetermined

spatial distribution and such a transport tool for said drops.

These purposes of the invention are achieved, as well as others which will become apparent upon reading the following description, with a transport tool for drops arranged in a predetermined spatial distribution, this tool being noteworthy in that it comprises at least one filiform support mounted on a frame clearing this support, said support presenting a plurality of areas which can be wetted by said liquid, distributed according to a predetermined distribution over its length, these wettable areas being separated by nonwettable sections of said support.

As will be seen below, all the wettable areas can be simultaneously loaded or unloaded of their liquid drops, which ensures very short operations of liquid transfer. The separation of the wettable areas can be very small, on the same order as that of the microwells on the plates mentioned above.

According to one embodiment of the tool according to the invention, the frame of the tool is rectangular, the support is filiform and stretched on this frame in successive parallel segments which are connected end-to-end, wettable areas being then arranged according to a regular two-dimensional planar distribution.

According to another embodiment of the tool according to the invention, the areas intended to remove or deposit the drops are defined by the intersections of two segments of the filiform support so as to ensure the wettability of the support only at the intersections, by capillarity. The invention also supplies a method for the transfer of the plurality of liquid drops between wells presenting a predetermined spatial distribution and a transport tool for said drops, this method being characterized in that a) a tool for the transport of drops according to the

invention is made, comprising a distribution of wettable areas according to said distribution of wells, and b) the distribution of wettable areas of said tool and the distribution of wells are superimposed in a relation of proximity causing the transfer of at least one of the drops carried by one of the distributions into the other distribution.

Other characteristics and advantages of the present invention will become apparent upon reading the following description and examining the drawings.

BRIEF DESCRIPTION OF THE FIGURES

- Figure 1 is a diagram of an embodiment of the filiform support of the tool according to the present invention,

- Figures 2A and 2B illustrate the method according to the invention, for loading liquid drops onto an equipped transport tool of the filiform support of Figure 1,

- Figure 3 is an enlarged diagram which explains the mechanism for the transfer of a distribution of drops carried by the tool of Figures 2A and 2B, into a distribution of microwells,

- Figures 4A and 4B illustrate the method according to the invention, applied to the transfer of the set of drops collected from a plate of microwells loaded with liquid,

- Figure 5 is a schematic perspective view of an apparatus for loading drops of different liquids onto a transport tool according to the invention,

- Figure 6 is a diagram of an element of the apparatus of Figure 5, useful for the description of the operation of this apparatus,

- Figure 7 is a schematic perspective view of a tool for transporting drops according to the invention, adapted to work in cooperation with the three-dimensional network of microwells,

- Figures 8A and 8B are schematic views which illustrate the operation of another embodiment of the tool for transporting drops according to the invention,

- Figure 9 is a schematic perspective view of a two-dimensional version of the tool illustrated in Figures 8A and 8B,

- Figure 10 is a plan view of yet another embodiment of the tool according to the present invention,

- Figure 11 represents a detail of a variant of the tool of Figure 9, and

- Figure 12 is a detail of a variant of the tool of Figure 10.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Reference is made to Figure 1 of the appended drawing, which shows a schematic representation of a filiform support 1 bearing liquid drops 2_1, 2_2, etc..., distributed over the length of the support. According to an embodiment of the invention which is represented schematically in Figure 3; this filiform support, or wire, 1 is mounted on a frame 3 in the shape of an arc which stretches the wire between its ends.

According to the present invention, the surface of the wire 3 is treated so that it is able to bear liquid drops only at predetermined places, distributed along the length of the wire.

Thus, when the wire 1 is immersed in a liquid 4 (see Figure 2A) filling a groove of a plate-reservoir 5, for example, and when the wire is then withdrawn from the groove (see Figure 2B), liquid remains on the wire in the

form of drops 2_1, 2_2, 2_3, etc..., present at the predetermined places or areas, two successive drops being separated by a nonwetted length or "wire section."

As an illustrative and nonlimiting example, it is possible to make such a wire 1 by covering a wire made of hydrophilic Inconel alloy and having a diameter of 20 µm with a very hydrophobic silane covering layer, followed by exposure of this layer through a mask to remove, by means of ultraviolet radiation, this layer in the areas 6_1, 6_2, 6_3, etc... (see Figure 1). The areas where the silane layer has been removed is hydrophilic, and therefore able to support drops 2_i of a liquid. In this manner it is possible to cause the wire to carry liquid drops with a very small volume, (e.g. 100-150 picoliters).

Alternatively and depending on the liquid to be transported, the wire 1 can be made of a hydrophobic material with a hydrophilic coating which is selectively removed outside of the areas 6_i that must bear drops. More generally, the surface of the wire is treated so as to ensure the wetting of predetermined areas of the surface of the wire by a given liquid and to prevent the wetting of the wire between these areas.

The assembly (1,3) constitutes a tool for the transport of liquid drops distributed over the wire 1 according to a predetermined distribution defined by the mask used during the exposure of the silane layer to ultraviolet radiation.

If one then moves the wire 1 towards the surface of the line of microwells 7_i, 7_{i+1}, etc..., hollowed out in the surface of the plate 8 (see Figure 3) of the type described in French Patent Application No. 95,13878 mentioned above, the distribution of the wells on the plate being identical to that of the drops on the wire, one can see that each one of the drops 2_i, 2_{i+1}, etc..., can be placed opposite a well 7_i, 7_{i+1}, etc..., by the use of

adequate means for alignment. Preferably, the spaces separating the bottoms of the wells receive a hydrophobic product 9. The drops 2_i then adhere to the bottoms of the well 6_i and they are completely transferred into them.

It now becomes clear that the transport tool (1,3) according to the invention allows a simple and simultaneous loading of a plurality of miniature wells, or microwells, 7_i with a liquid, and this [is true] even if the separation of the wells is very small (on the order of 100 μm), as is the case in the wells described in the above-mentioned French patent application. It is clear that the classic loading methods, for example, with micropipettes, use instruments which are too large to allow the simultaneous loading of such microwells, a problem which is, on the other hand, completely solved using a transport tool and the method for transfer according to the invention.

The latter thus is applied, notably, in cell cultures and biological assays carried out using microwell plates, cultures and trials which require notably the addition of nutrient liquid or reagent into the microwells. Such applications are, for example, the immunoenzymatic assays (ELISA), nucleic acid hybridization, viral titration, cloning and screening of colonies for protein production.

Reference is now made to Figures 4A and 4B to explain how the transport tool according to the invention also allows the extraction of liquid drops from microwell networks. In Figure 4A, a schematic representation is given of a line of microwells 7_i of the plate 8, these wells being provided with drops 2_i of a liquid of which samples must be extracted. Such extraction is necessary, for example, in cell cultures, when one must analyze products which are expressed or excreted in each microwell by live cells cultured in these wells, for example, for the production of monoclonal antibodies from hybridomas,

for the expression of inducible recombinant proteins or of viruses from various biological systems (bacteria, yeasts, animal or plant cells).

For this purpose, hydrophilic areas 6_i of the wire 1, perfectly dry, are placed opposite and in the vicinity of the wells 7_i, as shown in Figure 4A. As soon as the areas 6_i are immersed in the menisci of drops 2_i overflowing from the mouth of the wells onto plate 8, part $2'_i$ of these drops is transferred to the opposite hydrophilic area 6_i of the wire 1, as shown in Figure 4B. These samples $2'_i$ of the content of the wells can be transferred into microwells of other plates such as wells, for example, to make "fingerprint" plates used in microbiology.

Until now, the loading of the transport tool according to the invention with droplets of the same liquid has been described. In biological analysis, notably, it may be necessary to load adjacent wells with different liquids. To transfer such liquid droplets to the tool, the invention proposes the apparatus shown in Figure 5. The latter comprises a rectilinear arrangement of capillary tubes 10_i which have been drawn to a diameter on the order of 100 µm, for example, allowing their placement in a line with a separation identical to that of the hydrophilic area 6_i of the wire 1 of the support according to the invention.

As schematically shown in Figure 6, an optical fiber 11_i is associated with each capillary tube 10_i, with a microlens which focuses the light leaving the fiber into the liquid which fills the tube. It is known that the emission of a light pulse in the fiber causes the formation, at the open end or outlets 12_i of the tube 10_i of a droplet of the liquid. If, as shown in Figure 5, the wire 1 of the transport tool according to the invention is arranged opposite and in the vicinity of the outlet 12_i of the tubes, the hydrophilic areas of the wire being points

aligned with the outlets 12_i, the light pulses sent in predetermined fibers 11_i control the transfer of predetermined drops 2_i to the wire 1. The capillary tubes, which can be supplied with different liquids, make it possible for the drops 2_i carried by the wire 1 to have different compositions. It is then possible to transfer these drops using the tool according to the invention and, according to the mechanism described in connection with Figure 3, into different wells of a microwell plate. Such a transfer is useful for biological analysis (or in biology). An important application is the screening of synthetic or natural molecules, in the development of new drugs. The diagnostic tests in biological analysis constitute another example.

It is clear that the transfers of drops described above require a precise alignment of the wells with the hydrophilic areas of the wire 1 of the tool. Numerous known alignment means can be used for this purpose, notably means of the type used in photomechanical printing for the alignment of several color selections. These means consist of pegs (not represented) which are carried by one of the elements (the tool or the plate) and which penetrate into corresponding holes (not shown) hollowed out in the other device to place the two devices in a very precise relative arrangement.

Until now, means have been described which allow the transfer of microdrops between transport tool and only one row of microwells. The microwell plates described in the above-mentioned patent application comprise a plurality of adjacent rows of microwells. Thanks to the embodiment of the transport tool according to the invention which will now be described in connection with Figure 7, it is possible to proceed to simultaneous transfers of drops between this tool and several rows of microwells.

In Figure 7, the tool represented comprises an empty frame 3' which is essentially rectangular and equipped with gauge rods 13_i on both opposite edges, these gauge rods defining support points for a wire 1' which is passed around them so as to follow a planar crenelated trajectory consisting of parallel segments which are connected end to end. These segments are spaced at intervals, like the microwell rows of a plate 8 comprising a regular two-dimensional distribution of such microwells. As in the tool of figure 2B, the wire 1' carries hydrophilic areas presenting the same spatial distribution as the microwells of plate 8, the rest of the surface of the wire being hydrophobic.

An examination of Figure 7 shows that after a precise alignment of the rows of wells of the plate 8, obtained, for example, by means of pegs and holes (not shown), the tool represented allows a two-dimensional transfer of drops 2_{ij} between the set of the parallel segments of the wire 1' and the set of the rows of microwells of the plate. In this manner the number of liquid drops transferred or collected is conveniently multiplied when compared with the tool of Figure 2B.

The selective wettability necessary for the surface of the wire can be obtained, as seen above, by a local modification of this characteristic of the surface of the wire so that the liquid becomes attached to the area 6_i and so it is repelled by the intermediate parts of the wire between these areas. Other means could be used for the selective wetting of the wire, for example, the wire could be made locally highly porous, at the places where the liquid is to become attached to the wire. Liquid thus penetrates the pores made on the wire, so as to then retransfer, for example, by dilution, samples of this liquid into another liquid, or another analysis tool.

In Figure 8A, a very schematized representation of a transport tool is indicated, comprising a wire 1" mounted on a frame 3. In order to increase the wettability of the wire locally, it is intersected with other tangential wires or segments of wire $1''_1$, $1''_2$, $1''_3$, etc... at the level of the areas to be made wettable.

At the places where two wires intersect, the sampling of the drop is promoted by the phenomenon of capillarity. Trapped in a liquid, or in the liquid drops contained in the microwell 7_i of a row of such microwells, the intersections 14_i of the wires 1" and $1''_i$ each become loaded with a drop 2_i, as schematically represented in Figure 8B, the intervals between drops on the wire remaining dry.

Figure 9 represents another embodiment of the tool according to the invention, which applies the concept developed in connection with Figures 8A and 8B. In Figure 9, the tool represented comprises at least one wire 1" mounted on a frame 3" with the aid of pinholes 13_i, as in the embodiment of Figure 7. However, in this case, the wire segments stretched between two pinholes intersect along two orthogonal networks whose intersections trap, by capillarity, the drops 2_{ij} to be transferred. The latter can then be simultaneously transferred into the microwells of a plate 8 of such microwells, or they can be sampled in said microwells as seen above.

It should be noted that the wire 1" does not require the application of any local surface treatment, the latter often being expensive.

The present invention thereby provides means for the simultaneous transfer of a large number of liquid microdrops into or from a dense network of microwells which are inaccessible by the conventional means used for the much less dense networks of the prior art.

The present invention presents numerous other advantages. It allows ensuring reproducible transfers of liquid drops with respect to the volume of the drops. It provides for complete visibility of the operations of the transfer due to the fact that the transport tool is essentially transparent to an observer who carries out the transfer, for example, under microscope observation. The network of the wires of the tool is flexible and it can adapt to any defect in the flatness of the plate of microwells. The tool is inexpensive to manufacture and it can be discarded after one use, which is advantageous in biology or (or biological analysis). The live cells placed at the bottom of the wells remain separated from the wire of the tool and cannot be damaged by it. The alignment of the tool and of the network of microwells can be aided and facilitated by alignment pinholes and, in the case of the two-dimensional tools of Figures 7 and 9, by the use of a moiré effect. Finally, the invention allows the collection of samples by collecting samples from a gel or a deposit of samples on or in a gel layer.

Naturally, the invention is not limited to the described and represented embodiments which are only given as examples. Thus, it will be possible to make the network of filiform supports of the tool according to the invention by chemical engraving of the metallic sheet 14 as illustrated in Figure 10, where this engraving allows the cutting out of a network of supports in the form of wires 15_{ij} arranged, like those of Figure 9. Figure 10 also shows the holes 16_i used to align the tool 14 with a microwell plate, thanks to pinholes which are an integral part of this plate and engaging in these holes, as mentioned above.

In a variant, the tool of Figure 9 could comprise a double grid pattern of wires such as 17_1, 17_2, (see Figure 11), these double wires defining, at the intersections of

the grid, spaces which are capable of retaining drops of a larger volume. Using an engraving similar to that described in connection with the tool of Figure 10, it would be possible to form, at the intersections of the latter's supports in the form of wires, circular cutouts such as that (18) shown in Figure 12, which are capable of increasing the capillarity effect where the tool must support drops. Also, the invention is not limited to the transport of microdrops from or into microwells distributed with a separation on the order of 100 µm. It clearly also extends to wells of larger dimensions, distributed at a greater separation, for example, of a few millimeters. Larger drops are then obtained with wires having larger diameters, for example, 100-200 µm.

Claims

What is claimed is:

1. A tool for the transport of drops of liquids arranged according to a predetermined spatial distribution, characterized in that it comprises at least one filiform support (1;1';1",$1"_i$) of a predetermined length, mounted on a frame (3;3';3"), said support having a plurality of areas (6_i) which are wettable by said liquid and apportioned according to a predetermined distribution over its length said wettable areas (6_i) being separated by nonwettable sections of said support.

2. The tool according to Claim 1, characterized in that the support (1;1') consists of a metallic wire covered by a coating which is not wettable by said liquid, said coating being removed from the area (6_i) to be wetted by said liquid.

3. The tool according to Claim 1, characterized in that the support (1;1') consists of a metallic wire covered by a coating which is wettable by said liquid, said coating being removed outside of the areas to be wetted with said liquid.

4. The tool according to Claim 2, characterized in that the metallic wire is made of Inconel alloy and in that the coating is a silane.

5. The tool according to Claim 1, characterized in that the wettable areas (6_i) consist of porous areas of the surface of the support (1;1'), separated by nonporous sections of the support.

6. The tool according to any one of Claims 1-5, characterized in that the frame (3';3") is rectangular, the filiform support (1';1") being stretched on this frame in successive parallel segments which are connected end to end, the wettable areas (6_i) then being arranged according to a regular two-dimensional planar distribution.

7. The tool according to Claim 1, characterized in that the wettable areas (6_i) are defined by intersection of two segments (1", $1"_i$) of the filiform support which are capable, as a result of the capillary effect, to retain liquid drops at the intersections only.

8. The tool according to Claim 7, characterized in that it comprises two orthogonal networks of segments of filiform support, which are approximately superimposed in the same plane and define by their intersections a regular two-dimensional distribution of wettable areas.

9. The tool according to Claim 8, characterized in that said orthogonal networks of segments are cut into a metallic sheet (14), by chemical engraving.

10. The tool according to Claim 8, characterized in that the intersections of two networks are each perforated by an opening (18).

11. The tool according to Claim 8, characterized in that each one of said segments comprises two parallel and spaced supports in the form of wires (17_1, 17_2).

12. The tool according to any of the preceding claims, characterized in that the wettable areas are distributed with a separation on the order of approximately 100 µm.

13. A method for transferring a plurality of liquid drops (2_i) to wells (7_i) of a predetermined spatial distribution on a multiwell plate comprising the following steps:

a) providing a liquid transport tool having at least one filiform support mounted on a frame, said support having a distribution of wettable areas, separated by non wettable areas, said wettable areas apportioned and corresponding to said distribution of wells, and

b) placing and superimposing said distribution of wettable areas of said tool over said distribution of wells in such close proximity that at least one of the drops carried by said tool transfers to a corresponding well.

14. Method according to Claim 13, applied to the transfer of a distribution of drops carried by the transport tool (1,3) into a matching distribution of wells, characterized in that, to load the distribution of drops onto said tool, the filiform support (3) is entirely immersed in a reservoir (5) of the liquid to be transported.

15. Method according to Claim 13, applied to the transfer of a distribution of drops comprising drops of at least two different liquids, into a matching distribution of wells, characterized in that the different wettable areas (6_i) of the tool are loaded by being placed opposite the aligned outlets (12_i) of capillary tubes (10_i), at the separation of said areas, each tube (10_i) being filled with

a predetermined liquid, and the appearance of drops at the outlet of said tubes is activated selectively, for the purpose of wetting said areas.

16. Method according to Claim 13, applied to the sampling of fractions of liquids contained in a distribution of wells, characterized in that the wettable areas (6_i) of the transport tool are aligned with the corresponding well (7_i) of the distribution of wells, so as to wet said areas with the liquids contained in said wells.

17. Apparatus for loading drops onto a filiform support tool characterized in that it comprises at least one rectilinear arrangement of capillary tubes (10_i) each associated with means (11_i) to selectively control the formation of a drop of the liquid contained in the tube, at the outlet (12_i) of said tube, said outlets being arranged at the separation of the wettable areas (6_i) of the filiform support comprising the tool.

FIG.1

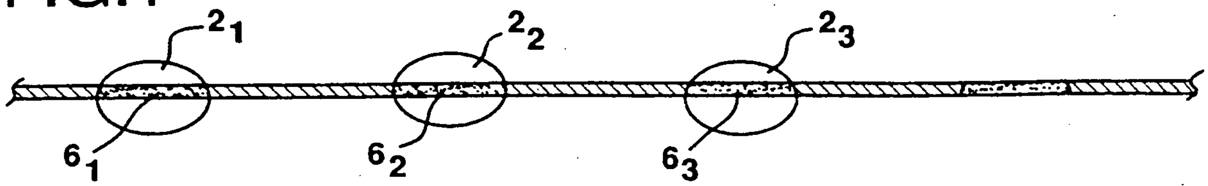


FIG.2A

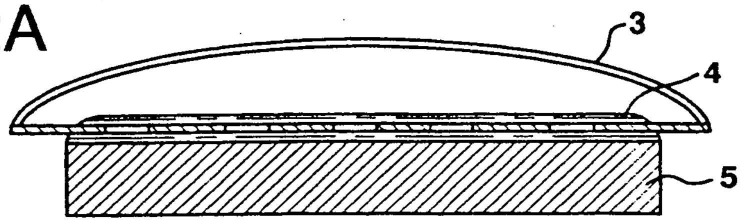


FIG.2B

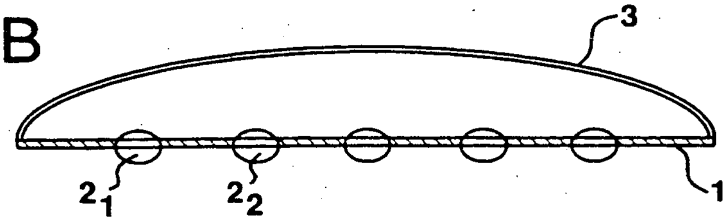


FIG.3

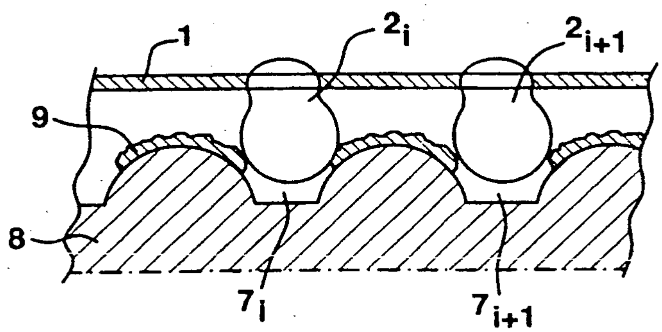


FIG.4A

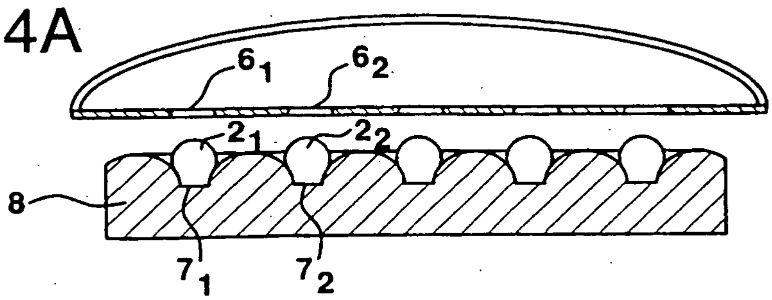


FIG.4B

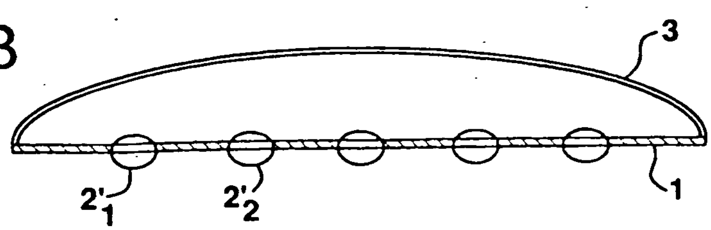


FIG.5

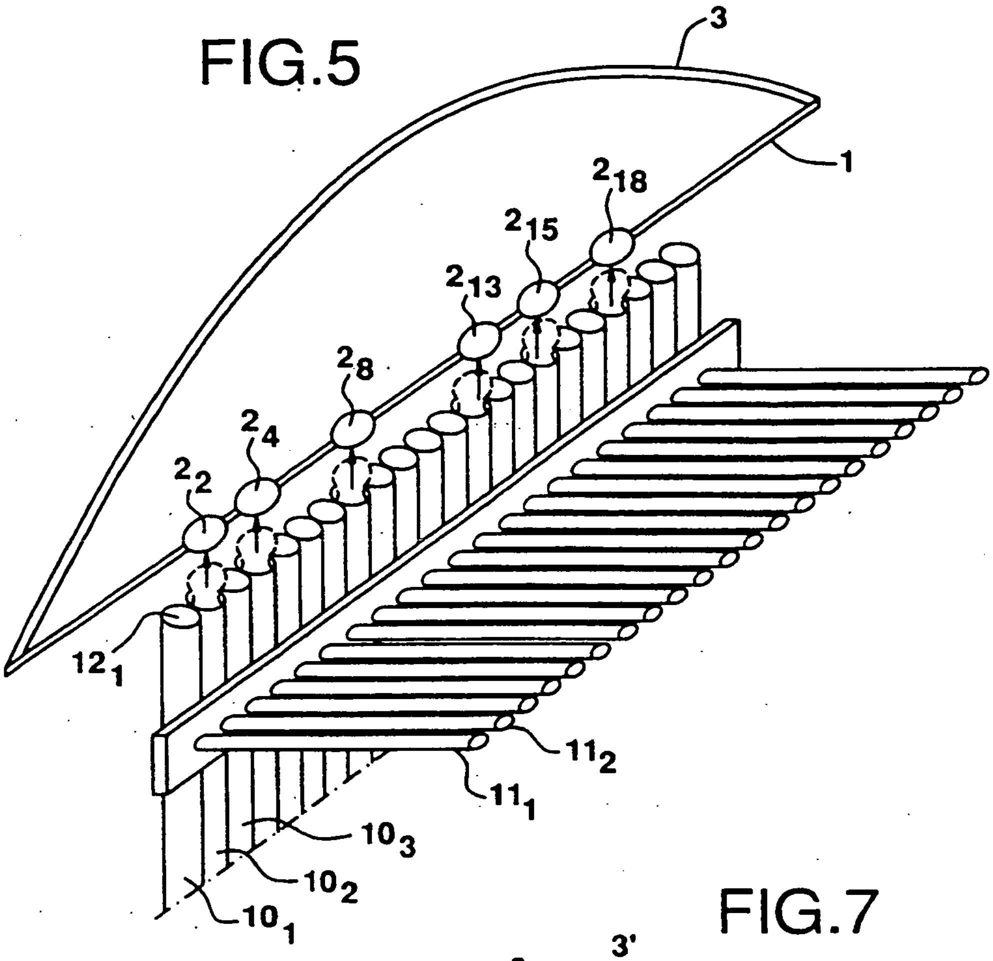


FIG.6

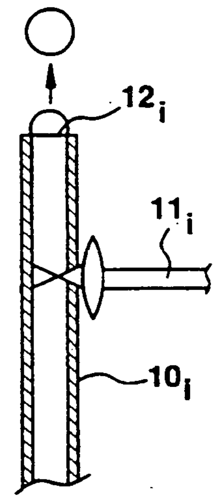


FIG.7

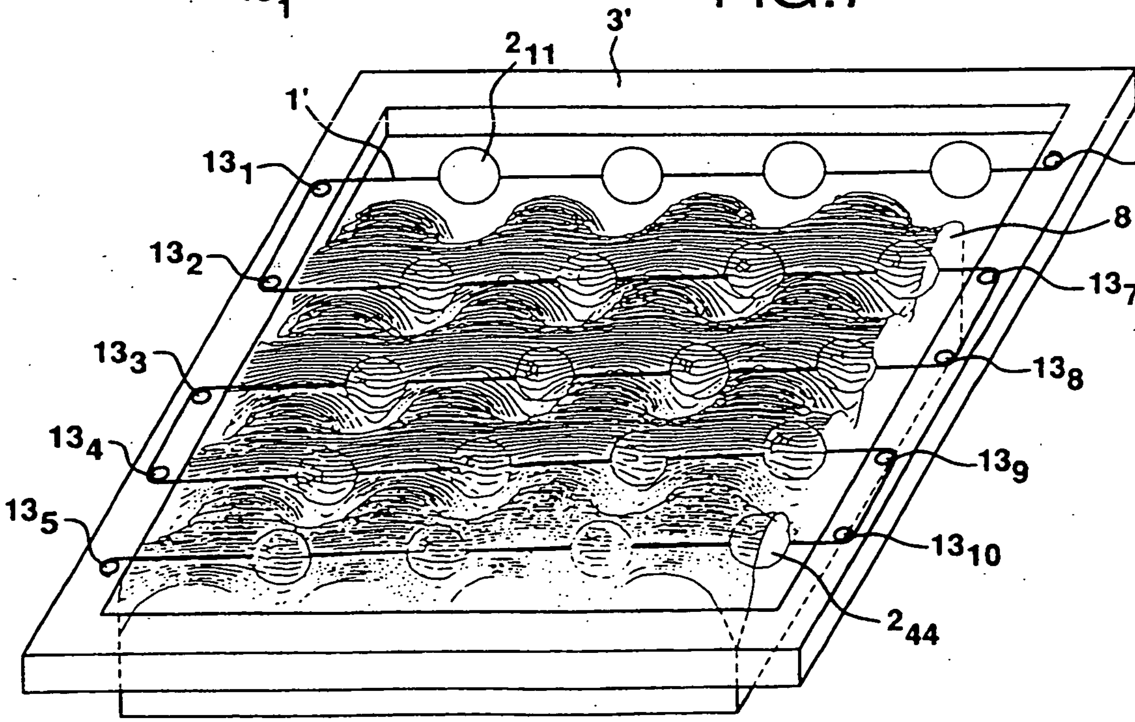


FIG.8A

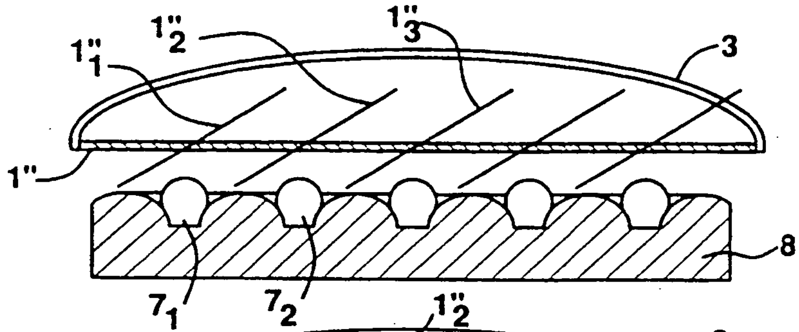


FIG.8B

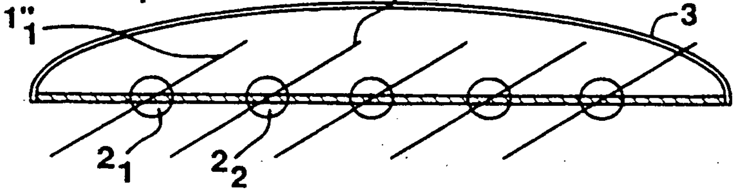


FIG.9

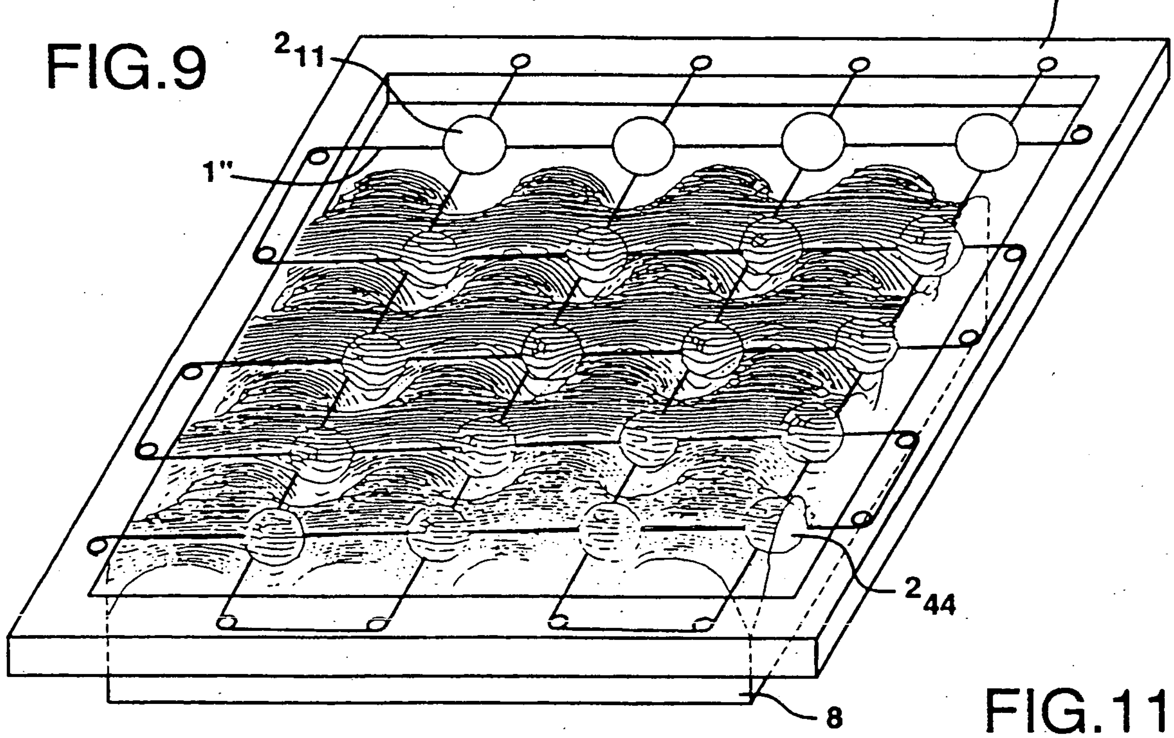


FIG.10

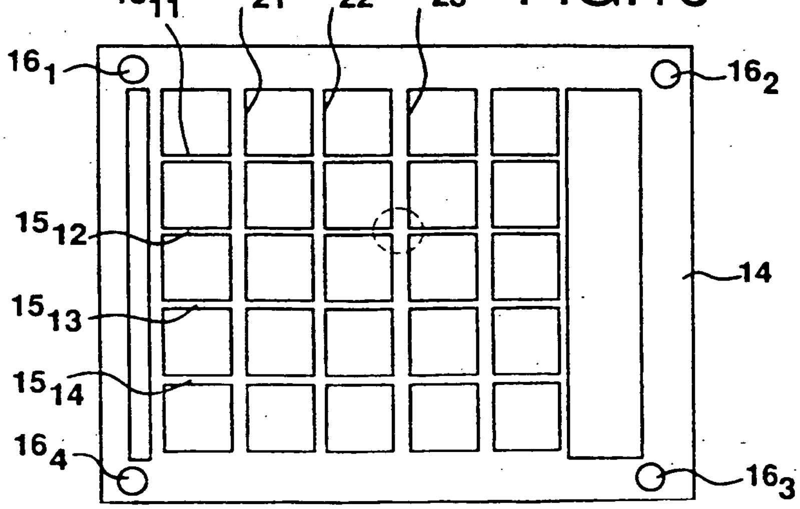


FIG.11

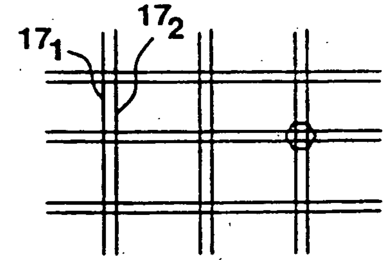
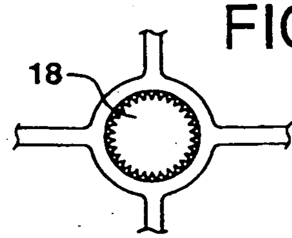


FIG.12



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(71) Applicant *(for all designated States except US)*: CORNING INCORPORATED [US/US]; 1 Riverfront Plaza, Corning, NY 14831 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: DANNOUX, Thierry, L., A. [FR/FR]; 18, résidence du Bel-Ebat, F-77210 Avon (FR).

(74) Agent: HERZFELD, Alexander, R.; Corning Incorporated, Patent Dept., SP FR 02-12, Corning, NY 14831 (US).

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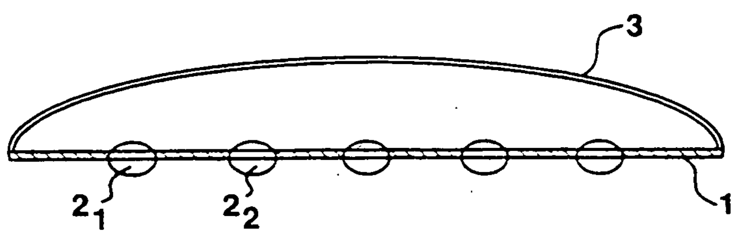

(57) Abstract

The tool (1, 3) is designed for the transport of drops (2_i) which are arranged according to a predetermined spatial distribution. It comprises at least one filiform support (1) mounted on a frame (3) clearing this support, said support presenting a plurality of the areas wettable by said liquid, distributed according to a predetermined distribution over its length, these wettable areas being separated from each other by nonwettable sections of said support (1). Application to cell cultures or tests on biological molecules.

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INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :G01N 1/10
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 073/863, 564.91

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 4,111,553 A (GARNYS) 05 September 1978 (05.09.78), see col. 1, lines 61-et seq.	1 2-17
Y	US 5,012,195 A (HARROLD) 30 April 1991 (30.04.91), see abstract.	1-17
Y	US 5,519,218 A (CHANG) 21 May 1996 (21.05.96), see col. 6, lines 52 et seq.	1-17
Y	US 4,008,154 A (RICHARDS ET AL.) 15 February 1977 (15.02.77), see abstract.	1-17
Y	US 4,396,287 A (HILDEBRAND ET AL.) 02 August 1983 (02.08.83), see col. 3.	1-17

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Name and mailing address of the ISA/US
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Facsimile No. (703) 305-3230

Authorized officer
NASHMIYA FAYYAZ Mary C Lilly
Telephone No. (703) 305-4900